FORM PTO-1390 (REV 10-94)	U S DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		13390.2USWO
		U S APPLICATION NO (If known, see 37 C F R 1 5) UNKNOWN 10/018719
INTERNATIONAL APPLICATION NO. PCT/EP00/05517	INTERNATIONAL FILING DATE JUNE 15, 2000	PRIORITY DATE CLAIMED JUNE 17, 1999

TITLE OF INVENTION

USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES

APPLICANT(S) FOR DO/EO/US

BECKER, Armin Johannes; STIEF, Christian George; UCKERT, Stefan; JONAS, Udo

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. [X] This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. [ ] This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. [X] This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(l).
4. [X] A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. [X] A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. [X] is transmitted herewith (required only if not transmitted by the International Bureau).
   b. [X] has been transmitted by the International Bureau.
   c. [ ] is not required, as the application was filed in the United States Receiving Office (RO/US)
6. [ ] A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. [X] Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. [ ] are transmitted herewith (required only if not transmitted by the International Bureau).
   b. [ ] have been transmitted by the International Bureau.
   c. [ ] have not been made; however, the time limit for making such amendments has NOT expired.
   d. [X] have not been made and will not be made.
8. [ ] A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. [X] An unsigned oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
10. [ ] A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern document(s) or information included:

11. [ ] An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. [ ] An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. [X] A FIRST preliminary amendment.
    [ ] A SECOND of SUBSEQUENT preliminary amendment.
14. [ ] A substitute specification.
15. [ ] A change of power of attorney and/or address letter.
16. [X] Other items or information: PCT/EP00/05517, PCT/ISA/210, PCT/IB/308; PCT/IPEA/409

U.S. APPLICATION NO (If known, see 37 C F R 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
UNKNOWN 10/018719	PCT/EP00/05517	13390.2USWO

17. [X] The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492(a) (1)-(5)):		
Search Report has been prepared by the EPO or JPO **$890.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492(a)(1)) **$710.00**		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) **$740.00**		
Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(3)) paid to USPTO **$1040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) **$100.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	**$890.00**	
Surcharge of **$130.00** for furnishing the oath or declaration later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(e)).	**$0**	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total claims	11 -20 =	0	X **$18.00**	**$0**	
Independent claims	2 -3 =	0	X **$84.00**	**$0**	
MULTIPLE DEPENDENT CLAIM(S) (if applicable)			+ **$260.00**	**$0**	
TOTAL OF ABOVE CALCULATIONS =				**$890.00**	
Reduction by 1/2 for filing by small entity, if applicable. Small entity status is claimed pursuant to 37 CFR 1.27				**$0**	
SUBTOTAL =				**$890.00**	
Processing fee of **$130.00** for furnishing the English translation later than [ ] 20 [ ] 30 months from the earliest claimed priority date (37 CFR 1.492(f). +				**$0**	
TOTAL NATIONAL FEE =				**$890.00**	
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +				**$0**	
TOTAL FEES ENCLOSED =				**$890.00**	
				Amount to be: refunded	**$0**
				charged	**$0**

a. [X] Check(s) in the amount of $890.00 to cover the above fees is enclosed.

b. [ ] Please charge my Deposit Account No. _____ in the amount of $ _____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. [X] The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 13-2725.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO
Ronald A. Daignault
MERCHANT & GOULD
P.O. Box 2903
Minneapolis, MN 55402-0903

SIGNATURE: Ronald A. Daignault

NAME: Ronald A. Daignault

REGISTRATION NUMBER: 25,968

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE 10/018719

Applicant: BECKER, et al.

Docket: 13390.2USWO

Title: USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES

CERTIFICATE UNDER 37 CFR 1 10
'Express Mail' mailing label number EL669945412US
Date of Deposit December 14, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1 10 and is addressed to the Commissioner for Patents, Washington, D.C. 20231

By _____
Name Chris Stordahl

BOX PATENT APPLICATION
Commissioner for Patents
Washington, D.C. 20231

Sir:

We are transmitting herewith the attached:

- ☒ Transmittal sheet, in duplicate, containing Certificate under 37 CFR 1.10.
- ☒ National Stage PCT Patent Application: Spec. 8 pgs; 11 claims; Abstract 1 pgs. The fee has been calculated as shown below in the 'Claims as Filed' table.
- ☒ 2 sheets of formal drawings
- ☒ An unsigned Combined Declaration and Power of Attorney
- ☒ A check in the amount of $890.00 to cover the Filing Fee
- ☒ Other: PCT/EP00/05517, Preliminary Amendment, PCT/ISA/210; PCT/IB/308; PCT/IPEA/409
- ☒ Return postcard

CLAIMS AS FILED

Number of Claims Filed		In Excess of:		Number Extra		Rate		Fee
Basic Filing Fee								$890.00
Total Claims								
11	-	20	=	0	x	18.00	=	$0.00
Independent Claims								
2	-	3	=	0	x	84.00	=	$0.00
MULTIPLE DEPENDENT CLAIM FEE								$0.00
TOTAL FILING FEE								$890.00

Please charge any additional fees or credit overpayment to Deposit Account No. 13-2725. A duplicate of this sheet is enclosed.

By: _____
Name: Ronald A. Daignault
Reg. No. 25,968
Initials: RADaignault/rw

MERCHANT & GOULD P.C.
P.O. Box 2903, Minneapolis, MN 55402-0903
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*235
52*

S/N unknown

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Becker, et al.	Docket No.:	13390.2USWO
Serial No.:	unknown	Filed:	concurrent herewith
Int'l Appln No.:	PCTEP00005517	Int'l Filing Date:	June 15, 2000
Title:	USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES		

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number: EL669945412US
Date of Deposit: December 14, 2001
I hereby certify that this paper or fee is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 and is addressed to the Commissioner for Patents, Washington, D C. 20231.

By: _____
Name: Chris Stordahl

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment:

IN THE ABSTRACT

Insert the attached Abstract page into the application as the last page thereof.

A courtesy copy of the present specification is enclosed herewith. However, the World Intellectual Property Office (WIPO) copy should be relied upon if it is already in the U.S. Patent Office.

REMARKS

A new abstract page is supplied to conform to that appearing on the publication page of the WIPO application, but the new Abstract is typed on a separate page as required by U.S. practice.

Applicants respectfully request that the preliminary amendment described herein be entered into the record prior to calculation of the filing fee and prior to examination and consideration of the above-identified application.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Ronald A. Daignault (Reg. No. 25,968), at (612) 371.5381.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Dated: December 14, 2001

By [signature]
Ronald A. Daignault
Reg. No. 25,968

RAD/rw

ABSTRACT
PCT/EP00/05517

USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES

The invention relates to the use of the human growth hormone (hGH, GH) either on its own or in combination with active substances which result in GH stimulation, have an effect which is analogous to GH or which promote the release of IGF-I in the production of medicaments which are used to treat sexual functional disturbances in both sexes. The invention also relates to a method for treating the above-mentioned dysfunctions.

#3

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Becker, et al.	Docket No.:	13390.2USWO
Serial No.:	10/018719	Filed:	December 14, 2001
Int'l Appln No.:	PCTEP00005517	Int'l Filing Date:	June 15, 2000
Title:	USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES		

CERTIFICATE UNDER 37 CFR 1.10
'Express Mail' mailing label number: EV072823491
Date of Deposit: March 21, 2002
I hereby certify that this paper or fee is being deposited with the United States Postal Service 'Express Mail Post Office To Addressee' service under 37 CFR 1.10 on the date indicated above and is addressed to the Commissioner of Patents and Trademarks, Washington, D.C. 20231.

By: Chris Stordahl

PRELIMINARY AMENDMENT

Box PCT
Assistant Commissioner for Patents
Washington, D. C. 20231

Dear Sir:

In connection with the above-identified application filed herewith, please enter the following preliminary amendment.

The present application was filed in the GERMAN language. Applicant now supplies the English translation of the application and the verified English translation of the specification are supplied herewith.

IN THE SPECIFICATION

Please amend the specification as follows:

Administration of Growth Hormone (hGH) for Therapy of Sexual Functional Disorders

Technical Field

[001] This invention concerns the introduction of human growth hormone (hGH, GH) for the manufacture of medicaments for the treatment of sexual functional disorders in both male and female patients as well as the specific methods of treatment undertaken.

Background of the Invention

[002] Symptoms indicating sexual functional disorders are, for example, lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction (ED). It could be deduced from certain cases that the basic aetiologies leading to these sexual functional disorders were due to a number of different reasons. Apart from the cases of mixed aetiologies, vascular (arterial, venous), psychogenic, neurogenic, medicamentous-induced and cavernous sexual functional disorders are also differentiated.

[003] Taking into consideration the nature of the underlying aetiologies, causal therapy of the sexual functional disorders is undertaken whenever possible. Up till now this method of therapy has only proved successful in the rare cases (e.g. by psychotherapy, hormone treatment, a change-over of medication) so that the main methods of therapy still remain unspecific.

[004] There are many different methods of therapy available for males with ED compared to those available for females with sexual functional disorders. These include oral, topical, intracavernous, intraurethral and also a combination of drugs. These methods do not constitute a causal therapy, rather the aim is to achieve a direct or indirect relaxation (flaccidity) of the corpus cavernosum smooth musculature and the penile arteries. Together with an increase of blood circulation, penile erection is achieved. Furthermore, the vacuum pump, arterial shunt procedure, venous closure operations and penile prosthesis implantations are also methods used for therapy. Until the introduction of sildenafil (VIAGRA®), the most widely used form of therapy involved the administration of intracavernous vasoactive substances. At the present time, sildenafil is used

as the so-called „first line therapy" providing there are no known contraindications. The oral phosphodiesterase type 5 inhibitor (PDE5) does not provide a basis for causal therapy. With the inhibition of PDE5, hydrolysis of cyclic guanosinmonophosphate (cGMP) of an intracellular second messenger is prohibited, resulting in relaxation of the corpus cavernosum smooth musculature. This effective mechanism is assumed beneficial for the increase of lubrication in women, however, recent studies have yet to prove its effectivity.

Summary of the Invention

[005] The aim of this innovative breakthrough was to present a new therapy for both males and females suffering from sexual functional disorders.

[006] Surprisingly, it has been shown that the growth hormone (hGH) plays an essential role in sexual stimulation, as an enormous unexpected increase of this hormone was seen to be present at the onset of sexual stimulation.

[007] The focal point of this breakthrough is therefore the use of hGH for the manufacture of medicaments for the treatment of sexual functional disorders in both males and females with e.g. lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction and for the therapy of the aforesaid functional disorders.

[008] Accordingly, the present invention is a method of treating female and male sexual functional disorders that includes administering an effective amount of growth hormone. The sexual functional disorder is manifested by a lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction; there is an insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists. A further aspect is the use of hGH for the therapy of functional disorders in synergic combination with effective substances which result in GH stimulation, induce a GH analogous effect or promote IGF-I release.

Brief Description of the Drawings

[010] **Figure 1** shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in cavernous and peripheral blood samples taken from 35 healthy probands during the four different phases of the penile erectile tissue (flaccidity, tumescence, rigidity and detumescence).

[011] **Figure 2** shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in the cavernous and peripheral blood samples during the three different penile phases (flaccidity, tumescence and detumescence) in 36 patients with erectile dysfunction. Rigidity was not achieved due to disorder of patient. The axis scale was selected as in Figure 1 in order to demonstrate clearly the difference ($P<0.05$).

[012] **Figure 3** shows the average values and standard deviations of the dose-dependent decrease in relaxation of 12 human corpus cavernosum strips after application of recombinant hGH.

[013] **Figure 4** shows the average values and standard deviations of dose-dependent increase of cyclic guanosinmonophasphate (cGMP) of 3 human corpus cavernosum strips respectively, following incubation with recombinant hGH or sodium nitroprusside (SNP). Incubation with SNP was carried out using a concentration of 0.01 and 1 µMol. For this reason, no value for SNP was achieved with 0.0001 µMol.

Detailed Description of the Invention

[014] In order to gain a better understanding of the physiology of a naturally induced erection and the pathophysiology of erectile dysfunction, a new method of investigation was developed. This involved detection of endogenous human neurotransmitters, neuromodulators and hormones which might have some connection with an erection or its sexual function. These new methods of investigation aim to improve the diagnostics and therapy (application of endogenous substances and causal therapy) for those patients with sexual functional disorders.

[015] Blood was taken simultaneously from the corpus cavernosum (CC, cavernous) and the cubital vein (CV, peripheral) in 35 healthy probands during the phases of flaccidity, tumescence, rigidity and detumescence. Audiovisual and tactile means were then provided to aid sexual stimulation (**Figure 1**). The procedure involving 36 patients with ED was identical to that of the healthy probands with the exception of blood withdrawal during the rigidity phase, (this penile erection phase cannot be achieved in patients with ED) (**Figure 2**). The hGH concentrations were determined with an immunoradiometric assay (IRMA). This form of investigation resulted in several new findings.

[016] The highest increase of hGH concentration was found during tumescence, namely the point in time when sexual stimulation is at its peak. The peripheral and cavernous hGH concentrations showed no significant differences in direct comparison with all penile phases. Peripheral blood withdrawal proved sufficient. When comparing the healthy probands with the patients, there were significant differences with regards to the hGH concentrations, in particular, a significantly reduced increase of the hGH concentration during the tumescence phase.

[017] These data show for the first time the surprising causal connection of hGH formed by the hypophysis with sexual stimulation and the resulting penile erection. The reduced expression of hGH on sexual stimulation in patients is further proof for the significance of this hormone, the lack of which is connected with sexual functional disorders and erectile dysfunction in this study.

[018] By means of extensive in vitro investigations using human corpus cavernosum (CC) tissue as well as the in vivo results described, important indications could be deduced for the possible physiological connections between hGH and penile erection. Organ bath experiments (in vitro method to evaluate the relaxing properties of substances) with human CC were carried out to assess dose-dependent relaxations following application of hGH (**Figure 3**).

[019] Incubation experiments (in vitro method to evaluate the content of cyclic nucleotides in tissues in response to drug exposition, in this case cGMP, after incubation with various substances) with human CC were shown to have dose-dependent higher cGMP concentrations

after application of hGH than was the case after incubation with sodium nitroprusside (SNP), a classic NO donator (**Figure 4**).

[020] Based on our human findings, it can be assumed that hGH plays a decisive role in sexual function (sexual stimulation), in particular, in penile erection. Furthermore, it was shown that the peripheral reaction of hGH induced an increase of cGMP, thereby physiologically forming a link between relaxation of CC with that of the ensuing erection. Due to the anatomical similarities in the structure of the penis and the clitoris and the physiological conformities regarding sexual stimulation (e.g. congestion of the genital organs mediated by neurotransmitter on relaxation of the smooth musculature), the described reaction of hGH in males must also apply to females too, since hGH is produced by the hypophysis in both sexes, therefore the same effect must also be evident in both sexes.

[021] With reference to the effect of hGH, it is already known that hGH does not focus on any particular tissue and that the activity and metabolism (anabolic) is increased in different tissues in both men and women. The growth hormone stimulates, for example, body growth (substitution in insufficient hGH-caused hyposomia) and protein metabolism (possible indication in cachexia, severe burn injuries and also anabolic abuse). Under the influence of hGH, an insulin-like growth factor I (IGF-I) is formed mainly in the liver but also in other tissues. This polypeptide (IGF-I) plays a significant mediating role in the process induced by hGH (Merimee T.J. and Grant M.B.: Growth hormone and its disorders. In: Principles and Practice of Endocrinology and Metabolism. Edited by Becker, K.L., Philadelphia, J.B. Lippincott Company, pp. 125-134, 1990).

[022] The most recent findings in humans show that there is a systemic increase of NO (nitric oxide) and cGMP under a substitution of recombinant produced hGH (r-hGH) in patients with hGH deficiency (Böger R.H. et al.: Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J. Clin. Invest. 98: 2706-2713, 1996). This NO-cGMP path presents a very important positive significance in achieving penile erection (Burnett A.L. et al.: Nitric oxide: a physiologic mediator or penile erection. Science 257: 905, 1993). Likewise, recent findings derived from animal experiments using rats were able to show that an increase of NOS (nitric oxide synthase)-

containing nerves (generating NO) in CC and dorsal penile nerves occurred under substitution of hGH. This took place despite initiation of neurogenic damage some weeks before (Jung G.W. et al.: Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous neurotomy in rats. J. Urol. 160: 1899-1904, 1998). The patent WO98/42361 (Human erectile dysfunction and methods of treatment) stems from these results and describes the indication of hGH therapy for the prevention and treatment of neurogenic erectile dysfunction of different aetiologies (condition following extensive pelvic operations or pelvic trauma, diabetes, alcoholism and aging process).

[023] Our findings on human models show for the first time a positive causal connection between sexual stimulation, increase of hGH and penile erection. The reduced (often totally lacking) increase of hGH in patients with ED emphasizes the importance of this hormone. The in vitro data conclude that the NO-cGMP path is activated by hGH, leading to relaxation of the CC, thus resulting in penile erection.

[024] The appropriate therapy for all patients (both sexes) with sexual functional disorders includes peripheral blood sample to determine the basal hGH concentration. This form of therapy is undertaken independent of the underlying aetiology(ies). Following this, a further blood sample is taken under sexual stimulation (audiovisual, tactile) in order to detect the stimulated hGH concentration. In cases of insufficient or no reaction at all to sexual stimulation (e.g. lubrication, penile erection) and inadequate increase of hGH concentration, a continuous, strictly controlled therapy with hGH should ensue for a certain period of time (e.g. 2 - 6 months).

[025] Suitable pharmaceutical preparations for therapy include solid or liquid forms of administration for oral intake, such as tablets, capsules or emulsions, parenteral forms of administration for injection or non-invasive application or transdermal topical systems, such as plasters, creams, gels, lotions or transdermal films. The administered amount for successful therapy lies between 0.01 and 500 mg per dosage unit; recommended is between 0.1 and 100 mg.

[026] Improvement of therapy outcome can be achieved by administration of a combination of medicaments containing, besides hGH, a synergic combination of substances which lead to GH stimulation, induce a GH analogous effect or promote IGF-I release.

[027] These substances do not have to be combined into one particular medication, but can be administered in separate suitable galenic preparations to be taken at the same time or taken separately according to the specific course of therapy. It is essential that the specialist instructs and informs the patient with regards to the suitable dosage or in which combination the medicaments should be taken, likewise which substance should be administered to ensure the best possible therapy outcome. Furthermore, it is permissible to combine several of the named substances to treat the individual patient accordingly.

[028] The suitable substances to be used as a combination therapy in order to achieve GH stimulation are familiar to the specialist. For example, arginine, alpha 1 and alpha 2-agonists, such as clonidine, norepinephrine or salbutamol, glucagon, pyridostigmine, galanine, GH-releasing hormone, NPY (neuropeptide Y) and dopamine agonists, such as apomorphine, quinpirole or cabergoline.

[029] Suitable substances which induce a GH analogous effect include, for instance, GHRP (growth hormone, releasing hexapeptide, hexareline), GH releasing peptide 1, 2, 6 and non-peptidergic agonists of growth hormone releasing peptide such as MK 0677, EP 51389 (2-methylalanyl-2-methyl-D-tryptophyl-2-methyl-D-tryptophanamide), L 692429 (3-amino-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]butanamide], or L 692585 (3-[[(2R)-2hydroxypropyl]amino]-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]-butanamide).

[030] Suitable substances which promote IGF-I release include, for example, cannabinoide such as e.g. HU-210 (3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol) or serotonine receptor agonists such as e.g. 8-OH

DPAT (8-hydroxy-2-dipropylamino)tetraline), or SC 53116 (4-amino-5-chloro-N-[[(1s,7aS)-hexahydro-1H-pyrrolizine-1-yl]methyl]-2-methoxy-benzamide)

IN THE CLAIMS

Please cancel claims 1-11 without prejudice or disclaimer. Add new claims 12-18.

12. (New) A method of treating femaled and male sexual functional disorders comprising administering an effective amount of a growth hormone, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

13. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that leads to GH stimulation.

14. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that induces a GH analogous effect.

15. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that promotes IGF-I release.

16. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that leads to growth hormone stimulation, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

17. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that induces a growth hormone analogous effect, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein

insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

18. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that promotes IGF-1 release, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

REMARKS

The above preliminary amendment is made to have the specification and claims conform to United States Patent and Trademark Office practice. Please refer to the Marked-Up Version attached herewith.

If a telephone conference would be helpful in resolving any issues concerning this communication, please contact Applicants' primary attorney-of record, Ronald A. Daignault (Reg. No. 25,968), at (612) 371.5381.

Please charge any additional fees or credit any overpayment to Deposit Account No. 13-2725.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

Dated: March 21, 2002

By Ronald A. Daignault
Ronald A. Daignault
Reg. No. 25,968

RAD/rw

(MARKED UP VERSION)

Administration of Growth Hormone (hGH) for Therapy of Sexual Functional Disorders

Technical Field

[001] This invention concerns the introduction of human growth hormone (hGH, GH) for the manufacture of medicaments for the treatment of sexual functional disorders in both male and female patients as well as the specific methods of treatment undertaken.

Background of the Invention

[002] Symptoms indicating sexual functional disorders are, for example, lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction (ED). It could be deduced from certain cases that the basic aetiologies leading to these sexual functional disorders were due to a number of different reasons. Apart from the cases of mixed aetiologies, vascular (arterial, venous), psychogenic, neurogenic, medicamentous-induced and cavernous sexual functional disorders are also differentiated.

[003] Taking into consideration the nature of the underlying aetiologies, causal therapy of the sexual functional disorders is undertaken whenever possible. Up till now this method of therapy has only proved successful in the rare cases (e.g. by psychotherapy, hormone treatment, a change-over of medication) so that the main methods of therapy still remain unspecific.

[004] There are many different methods of therapy [are] available for males with ED compared to those available for females with sexual functional disorders. These include oral, topical, intracavernous, intraurethral and also a combination of drugs. These methods do not constitute a causal therapy, rather the aim is to achieve a direct or indirect relaxation (flaccidity) of the corpus cavernosum smooth musculature and the penile arteries. Together with an increase of blood circulation, penile erection is achieved. Furthermore, the vacuum pump, arterial shunt procedure, venous closure operations and penile prosthesis implantations are also methods used for therapy. Until the introduction of sildenafil (VIAGRA®), the most widely used form of therapy involved the administration of intracavernous vasoactive substances. At the present time, sildenafil is used as the so-called „first line therapy" providing there are no known contraindications. The oral phosphodiesterase type 5 inhibitor (PDE5) does not provide a basis for causal therapy. With the inhibition of PDE5, hydrolysis

of cyclic guanosinmonophosphate (cGMP) of an intracellular second messenger is prohibited, resulting in relaxation of the corpus cavernosum smooth musculature. This effective mechanism is assumed beneficial for the increase of lubrication in women, however, recent studies have yet to prove its effectivity.

Summary of the Invention

[005] The aim of this innovative breakthrough was to present a new therapy for both males and females suffering from sexual functional disorders.

[006] Surprisingly, it has been shown that the growth hormone (hGH) plays an essential role in sexual stimulation, as an enormous unexpected increase of this hormone was seen to be present at the onset of sexual stimulation.

[007] The focal point of this breakthrough is therefore the use of hGH for the manufacture of medicaments for the treatment of sexual functional disorders in both males and females with e.g. lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction and for the therapy of the aforesaid functional disorders.

[008] Accordingly, the present invention is a method of treating female and male sexual functional disorders that includes administering an effective amount of growth hormone. The sexual functional disorder is manifested by a lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction; there is an insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists. A further [issue] aspect is the use of hGH for the therapy of functional disorders in synergic combination with effective substances which result in GH stimulation, induce a GH analogous effect or promote IGF-I release.

[009] [The scientific results described are emphasized as follows:]

Brief Description of the Drawings

[010] **Figure 1** shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in cavernous and peripheral blood samples taken from 35 healthy probands during the four different phases of the penile erectile tissue (flaccidity, tumescence, rigidity and detumescence).

[011] **Figure 2** shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in the cavernous and peripheral blood samples during the three different penile phases (flaccidity, tumescence and detumescence) in 36 patients with erectile dysfunction. Rigidity was not achieved due to disorder of patient. The axis scale was selected as in Figure 1 in order to demonstrate clearly the difference ($P<0.05$).

[012] **Figure 3** shows the average values and standard deviations of the dose-dependent decrease in relaxation of 12 human corpus cavernosum strips after application of recombinant hGH.

[013] **Figure 4** shows the average values and standard deviations of dose-dependent increase of cyclic guanosinmonophasphate (cGMP) of 3 human corpus cavernosum strips respectively, following incubation with recombinant hGH or sodium nitroprusside (SNP). Incubation with SNP was carried out using a concentration of 0.01 and 1 µMol. For this reason, no value for SNP was achieved with 0.0001 µMol.

Detailed Description of the Invention

[014] In order to gain a better understanding of the physiology of a naturally induced erection and the pathophysiology of erectile dysfunction, a new method of investigation was developed. This involved detection of endogenous human neurotransmitters, neuromodulators and hormones which might have some connection with an erection or its sexual function. These new methods of investigation aim to improve the diagnostics and therapy (application of endogenous substances and causal therapy) for those patients with sexual functional disorders.

[015] Blood was taken simultaneously from the corpus cavernosum (CC, cavernous) and the cubital vein (CV, peripheral) in 35 healthy probands during the phases of flaccidity, tumescence, rigidity and detumescence. Audiovisual and tactile means were then provided to aid sexual stimulation (**Figure 1**). The procedure involving 36 patients with ED was identical to that of the healthy probands with the exception of blood withdrawal during the rigidity phase, (this penile erection phase cannot be achieved in patients with ED) (**Figure 2**). The hGH concentrations were determined with an immunoradiometric assay (IRMA). This form of investigation resulted in several new findings.

[016] [1.]The highest increase of hGH concentration was found during tumescence, namely the point in time when sexual stimulation is at its peak. [2.]The peripheral and cavernous hGH concentrations showed no significant differences in direct comparison with all penile phases. Peripheral blood withdrawal proved sufficient. [3.]When comparing the healthy probands with the patients, there were significant differences with regards to the hGH concentrations, in particular, a significantly reduced increase of the hGH concentration during the tumescence phase.

[017] These data show for the first time the surprising causal connection of hGH formed by the hypophysis with sexual stimulation and the resulting penile erection. The reduced expression of hGH on sexual stimulation in patients is further proof for the significance of this hormone, the lack of which is connected with sexual functional disorders and erectile dysfunction in this study.

[018] By means of extensive in vitro investigations using human corpus cavernosum (CC) tissue as well as the in vivo results described, important indications could be deduced for the possible physiological connections between hGH and penile erection. [1.]Organ bath experiments (in vitro method to evaluate the relaxing properties of substances) with human CC were carried out to assess dose-dependent relaxations following application of hGH (**Figure 3**).

[019] [2.]Incubation experiments (in vitro method to evaluate the content of cyclic nucleotides in tissues in response to drug exposition, in this case cGMP, after incubation with various substances) with human CC were shown to have dose-dependent higher cGMP concentrations after application of hGH than was the case after incubation with sodium nitroprusside (SNP), a classic NO donator (**Figure 4**).

[020] Based on our human findings, it can be assumed that hGH plays a decisive role in sexual function (sexual stimulation), in particular, in penile erection. Furthermore, it was shown that the peripheral reaction of hGH induced an increase of cGMP, thereby physiologically forming a link between relaxation of CC with that of the ensuing erection. Due to the anatomical similarities in the structure of the penis and the clitoris and the physiological conformities regarding sexual stimulation (e.g. congestion of the genital organs mediated by neurotransmitter on relaxation of the smooth musculature), the described reaction

of hGH in males must also apply to females too, since hGH is produced by the hypophysis in both sexes, therefore the same effect must also be evident in both sexes.

[021] With reference to the effect of hGH, it is already known that hGH does not focus on any particular tissue and that the activity and metabolism (anabolic) is increased in different tissues in both men and women. The growth hormone stimulates, for example, body growth (substitution in insufficient hGH-caused hyposomia) and protein metabolism (possible indication in cachexia, severe burn injuries and also anabolic abuse). Under the influence of hGH, an insulin-like growth factor I (IGF-I) is formed mainly in the liver but also in other tissues. This polypeptide (IGF-I) plays a significant mediating role in the process induced by hGH (Merimee T.J. and Grant M.B.: Growth hormone and its disorders. In: Principles and Practice of Endocrinology and Metabolism. Edited by Becker, K.L., Philadelphia, J.B. Lippincott Company, pp. 125-134, 1990).

[022] The most recent findings in humans show that there is a systemic increase of NO (nitric oxide) and cGMP under a substitution of recombinant produced hGH (r-hGH) in patients with hGH deficiency (Böger R.H. et al.: Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J. Clin. Invest. 98: 2706-2713, 1996). This NO-cGMP path presents a very important positive significance in achieving penile erection (Burnett A.L. et al.: Nitric oxide: a physiologic mediator or penile erection. Science 257: 905, 1993). Likewise, recent findings derived from animal experiments using rats were able to show that an increase of NOS (nitric oxide synthase)-containing nerves (generating NO) in CC and dorsal penile nerves occurred under substitution of hGH. This took place despite initiation of neurogenic damage some weeks before (Jung G.W. et al.: Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous neurotomy in rats. J. Urol. 160: 1899-1904, 1998). The patent WO98/42361 (Human erectile dysfunction and methods of treatment) stems from these results and describes the indication of hGH therapy for the prevention and treatment of neurogenic erectile dysfunction of different aetiologies (condition following extensive pelvic operations or pelvic trauma, diabetes, alcoholism and aging process).

[023] Our findings on human models show for the first time a positive causal connection between sexual stimulation, increase of hGH and penile erection. The reduced (often totally lacking) increase of hGH in patients with ED emphasizes the importance of this hormone.

The in vitro data conclude that the NO-cGMP path is activated by hGH, leading to relaxation of the CC, thus resulting in penile erection.

[024] The appropriate therapy for all patients (both sexes) with sexual functional disorders includes peripheral blood sample to determine the basal hGH concentration. This form of therapy is undertaken independent of the underlying aetiology(ies). Following this, a further blood sample is taken under sexual stimulation (audiovisual, tactile) in order to detect the stimulated hGH concentration. In cases of insufficient or no reaction at all to sexual stimulation (e.g. lubrication, penile erection) and inadequate increase of hGH concentration, a continuous, strictly controlled therapy with hGH should ensue for a certain period of time (e.g. 2 - 6 months).

[025] Suitable pharmaceutical preparations for therapy include solid or liquid forms of administration for oral intake, such as tablets, capsules or emulsions, parenteral forms of administration for injection or non-invasive application or transdermal topical systems, such as plasters, creams, gels, lotions or transdermal films. The administered amount for successful therapy lies between 0.01 and 500 mg per dosage unit; recommended is between 0.1 and 100 mg.

[026] Improvement of therapy outcome can be achieved by administration of a combination of medicaments containing, besides hGH, a synergic combination of substances which lead to GH stimulation, induce a GH analogous effect or promote IGF-I release.

[027] These substances do not have to be combined into one particular medication, but can be administered in separate suitable galenic preparations to be taken at the same time or taken separately according to the specific course of therapy. It is essential that the specialist instructs and informs the patient with regards to the suitable dosage or in which combination the medicaments should be taken, likewise which substance should be administered to ensure the best possible therapy outcome. Furthermore, it is permissible to combine several of the named substances to treat the individual patient accordingly.

[028] The suitable substances to be used as a combination therapy in order to achieve GH stimulation are familiar to the specialist. For example, arginine, alpha 1 and alpha 2-agonists, such as clonidine, norepinephrine or salbutamol, glucagon, pyridostigmine, galanine, GH-

releasing hormone, NPY (neuropeptide Y) and dopamine agonists, such as apomorphine, quinpirole or cabergoline.

[029] Suitable substances which induce a GH analogous effect include, for instance, GHRP (growth hormone, releasing hexapeptide, hexareline), GH releasing peptide 1, 2, 6 and non-peptidergic agonists of growth hormone releasing peptide such as MK 0677, EP 51389 (2-methylalanyl-2-methyl-D-tryptophyl-2-methyl-D-tryptophanamide), L 692429 (3-amino-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]butanamide], or L 692585 (3-[[(2R)-2hydroxypropyl]amino]-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]-butanamide).

[030] Suitable substances which promote IGF-I release include, for example, cannabinoide such as e.g. HU-210 (3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol) or serotonine receptor agonists such as e.g. 8-OH DPAT (8-hydroxy-2-dipropylamino)tetraline), or SC 53116 (4-amino-5-chloro-N-[[(1s,7aS)-hexahydro-1H-pyrrolizine-1-yl]methyl]-2-methoxy-benzamide).

WE CLAIM:

Please cancel claims 1-11 without prejudice or disclaimer and add claims 12-18.

12. (New) A method of treating femaled and male sexual functional disorders comprising administering an effective amount of a growth hormone, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

13. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that leads to GH stimulation.

14. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that induces a GH analogous effect.

15. (New) The method of claim 12, wherein the growth hormone is administered in combination with a substance that promotes IGF-I release.

16. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that leads to growth hormone stimulation, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

17. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that induces a growth hormone analogous effect, wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

18. (New) A method of treating female and male sexual functional disorders comprising administering an effective amount of a substance that promotes IGF-1 release,

wherein the sexual functional disorder is manifested by lack or loss of libido, problems relating to orgasms, insufficient lubrication, or erectile dysfunction and wherein insufficient increase in hGH concentration occurs during sexual stimulation or a hGH deficiency exists.

#3

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14.12.01

To whom it may concern

I, Nicola van Dornick, Personal Assistant, with residence at Rambergstr. 29, 30161 Hannover, Germany, herewith declare that I am well acquainted with the German and the English language and that the translated document is a true, correct, and complete English translation of the German International Patent Application No. WO 00/78328.

Hannover, Germany, 14.12.01

Nicola van Dornick

Administration of Growth Hormone (hGH) for Therapy of Sexual Functional Disorders

This invention concerns the introduction of human growth hormone (hGH, GH) for the manufacture of medicaments for the treatment of sexual functional disorders in both male and female patients as well as the specific methods of treatment undertaken.

Symptoms indicating sexual functional disorders are, for example, lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction (ED). It could be deduced from certain cases that the basic aetiologies leading to these sexual functional disorders were due to a number of different reasons. Apart from the cases of mixed aetiologies, vascular (arterial, venous), psychogenic, neurogenic, medicamentous-induced and cavernous sexual functional disorders are also differentiated.

Taking into consideration the nature of the underlying aetiologies, causal therapy of the sexual functional disorders is undertaken whenever possible. Up till now this method of therapy has only proved successful in the rare cases (e.g. by psychotherapy, hormone treatment, a change-over of medication) so that the main methods of therapy still remain unspecific.

There are many different methods of therapy are available for males with ED compared to those available for females with sexual functional disorders. These include oral, topical, intracavernous, intraurethral and also a combination of drugs. These methods do not constitute a causal therapy, rather the aim is to achieve a direct or indirect relaxation (flaccidity) of the corpus cavernosum smooth musculature and the penile arteries. Together with an increase of blood circulation, penile erection is achieved. Furthermore, the vacuum pump, arterial shunt procedure, venous closure operations and penile prosthesis implantations are also methods used for therapy. Until the introduction of sildenafil (VIAGRA®), the most widely used form of therapy involved the administration of intracavernous vasoactive substances. At the present time, sildenafil is used as the so-called „first line therapy" providing there are no known contraindications. The oral phosphodiesterase type 5 inhibitor (PDE5) does not provide a basis for causal therapy. With the inhibition of PDE5, hydrolysis of cyclic guanosinmonophosphate (cGMP) of an intracellular second messenger is prohibited, resulting in relaxation of the corpus cavernosum smooth musculature. This effective mechanism is assumed beneficial for the increase of lubrication in women, however, recent studies have yet to prove its effectivity.

The aim of this innovative breakthrough was to present a new therapy for both males and females suffering from sexual functional disorders.

Surprisingly, it has been shown that the growth hormone (hGH) plays an essential role in sexual stimulation, as an enormous unexpected increase of this hormone was seen to be present at the onset of sexual stimulation.

The focal point of this breakthrough is therefore the use of hGH for the manufacture of medicaments for the treatment of sexual functional disorders in both males and females with e.g. lack or loss of libido, problems relating to orgasms, insufficient lubrication and erectile dysfunction and for the therapy of the aforesaid functional disorders.

A further issue is the use of hGH for the therapy of functional disorders in synergic combination with effective substances which result in GH stimulation, induce a GH analogous effect or promote IGF-I release.

The scientific results described are emphasized as follows:

Figure 1 shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in cavernous and peripheral blood samples taken from 35 healthy probands during the four different phases of the penile erectile tissue (flaccidity, tumescence, rigidity and detumescence).

Figure 2 shows the average values and standard deviations of the growth hormone (hGH) concentrations (ng/ml) in the cavernous and peripheral blood samples during the three different penile phases (flaccidity, tumescence and detumescence) in 36 patients with erectile dysfunction. Rigidity was not achieved due to disorder of patient. The axis scale was selected as in Figure 1 in order to demonstrate clearly the difference ($P<0.05$).

Figure 3 shows the average values and standard deviations of the dose-dependent decrease in relaxation of 12 human corpus cavernosum strips after application of recombinant hGH.

Figure 4 shows the average values and standard deviations of dose-dependent increase of cyclic guanosinmonophasphate (cGMP) of 3 human corpus cavernosum strips respectively, following incubation with recombinant hGH or sodium nitroprusside (SNP). Incubation with SNP was carried out using a concentration of 0.01 and 1 µMol. For this reason, no value for SNP was achieved with 0.0001 µMol.

In order to gain a better understanding of the physiology of a naturally induced erection and the pathophysiology of erectile dysfunction, a new method of investigation was developed. This involved detection of endogenous human neurotransmitters, neuromodulators and hormones which might have some connection with an erection or its sexual function. These

new methods of investigation aim to improve the diagnostics and therapy (application of endogenous substances and causal therapy) for those patients with sexual functional disorders.

Blood was taken simultaneously from the corpus cavernosum (cavernous) and the cubital vein (peripheral) in 35 healthy probands during the phases of flaccidity, tumescence, rigidity and detumescence. Audiovisual and tactile means were then provided to aid sexual stimulation (Figure 1). The procedure involving 36 patients with ED was identical to that of the healthy probands with the exception of blood withdrawal during the rigidity phase, (this penile erection phase cannot be achieved in patients with ED) (Figure 2). The hGH concentrations were determined with an immunoradiometric assay (IRMA). This form of investigation resulted in several new findings.

1. The highest increase of hGH concentration was found during tumescence, namely the point in time when sexual stimulation is at its peak.

2. The peripheral and cavernous hGH concentrations showed no significant differences in direct comparison with all penile phases. Peripheral blood withdrawal proved sufficient.

3. When comparing the healthy probands with the patients, there were significant differences with regards to the hGH concentrations, in particular, a significantly reduced increase of the hGH concentration during the tumescence phase.

These data show for the first time the surprising causal connection of hGH formed by the hypophysis with sexual stimulation and the resulting penile erection. The reduced expression of hGH on sexual stimulation in patients is further proof for the significance of this hormone, the lack of which is connected with sexual functional disorders and erectile dysfunction in this study.

By means of extensive in vitro investigations using human corpus cavernosum (CC) tissue as well as the in vivo results described, important indications could be deduced for the possible physiological connections between hGH and penile erection.

1. Organ bath experiments (in vitro method to evaluate the relaxing properties of substances) with human CC were carried out to assess dose-dependent relaxations following application of hGH (Figure 3).

2. Incubation experiments (in vitro method to evaluate the content of cyclic nucleotides in tissues in response to drug exposition, in this case cGMP, after incubation with various

substances) with human CC were shown to have dose-dependent higher cGMP concentrations after application of hGH than was the case after incubation with sodium nitroprusside (SNP), a classic NO donator (Figure 4).

Based on our human findings, it can be assumed that hGH plays a decisive role in sexual function (sexual stimulation), in particular, in penile erection. Furthermore, it was shown that the peripheral reaction of hGH induced an increase of cGMP, thereby physiologically forming a link between relaxation of CC with that of the ensuing erection. Due to the anatomical similarities in the structure of the penis and the clitoris and the physiological conformities regarding sexual stimulation (e.g. congestion of the genital organs mediated by neurotransmitter on relaxation of the smooth musculature), the described reaction of hGH in males must also apply to females too, since hGH is produced by the hypophysis in both sexes, therefore the same effect must also be evident in both sexes.

With reference to the effect of hGH, it is already known that hGH does not focus on any particular tissue and that the activity and metabolism (anabolic) is increased in different tissues in both men and women. The growth hormone stimulates, for example, body growth (substitution in insufficient hGH-caused hyposomia) and protein metabolism (possible indication in cachexia, severe burn injuries and also anabolic abuse). Under the influence of hGH, an insulin-like growth factor I (IGF-I) is formed mainly in the liver but also in other tissues. This polypeptide (IGF-I) plays a significant mediating role in the process induced by hGH (Merimee T.J. and Grant M.B.: Growth hormone and its disorders. In: Principles and Practice of Endocrinology and Metabolism. Edited by Becker, K.L., Philadelphia, J.B. Lippincott Company, pp. 125-134, 1990).

The most recent findings in humans show that there is a systemic increase of NO (nitric oxide) and cGMP under a substitution of recombinant produced hGH (r-hGH) in patients with hGH deficiency (Böger R.H. et al.: Nitric oxide may mediate the hemodynamic effects of recombinant growth hormone in patients with acquired growth hormone deficiency. J. Clin. Invest. 98: 2706-2713, 1996). This NO-cGMP path presents a very important positive significance in achieving penile erection (Burnett A.L. et al.: Nitric oxide: a physiologic mediator or penile erection. Science 257: 905, 1993). Likewise, recent findings derived from animal experiments using rats were able to show that an increase of NOS (nitric oxide synthase)-containing nerves (generating NO) in CC and dorsal penile nerves occurred under substitution of hGH. This took place despite initiation of neurogenic damage some weeks before (Jung G.W. et al.: Growth hormone enhances regeneration of nitric oxide synthase-containing penile nerves after cavernous neurotomy in rats. J. Urol. 160: 1899-1904, 1998). The patent WO98/42361 (Human erectile dysfunction and methods of treatment) stems from these results and describes the indication of hGH therapy for the prevention and treatment of

neurogenic erectile dysfunction of different aetiologies (condition following extensive pelvic operations or pelvic trauma, diabetes, alcoholism and aging process).

Our findings on human models show for the first time a positive causal connection between sexual stimulation, increase of hGH and penile erection. The reduced (often totally lacking) increase of hGH in patients with ED emphasizes the importance of this hormone. The in vitro data conclude that the NO-cGMP path is activated by hGH, leading to relaxation of the CC, thus resulting in penile erection.

The appropriate therapy for all patients (both sexes) with sexual functional disorders includes peripheral blood sample to determine the basal hGH concentration. This form of therapy is undertaken independent of the underlying aetiology(ies). Following this, a further blood sample is taken under sexual stimulation (audiovisual, tactile) in order to detect the stimulated hGH concentration. In cases of insufficient or no reaction at all to sexual stimulation (e.g. lubrication, penile erection) and inadequate increase of hGH concentration, a continuous, strictly controlled therapy with hGH should ensue for a certain period of time (e.g. 2 - 6 months).

Suitable pharmaceutical preparations for therapy include solid or liquid forms of administration for oral intake, such as tablets, capsules or emulsions, parenteral forms of administration for injection or non-invasive application or transdermal topical systems, such as plasters, creams, gels, lotions or transdermal films. The administered amount for successful therapy lies between 0.01 and 500 mg per dosage unit; recommended is between 0.1 and 100 mg.

Improvement of therapy outcome can be achieved by administration of a combination of medicaments containing, besides hGH, a synergic combination of substances which lead to GH stimulation, induce a GH analogous effect or promote IGF-I release.

These substances do not have to be combined into one particular medication, but can be administered in separate suitable galenic preparations to be taken at the same time or taken separately according to the specific course of therapy. It is essential that the specialist instructs and informs the patient with regards to the suitable dosage or in which combination the medicaments should be taken, likewise which substance should be administered to ensure the best possible therapy outcome. Furthermore, it is permissible to combine several of the named substances to treat the individual patient accordingly.

The suitable substances to be used as a combination therapy in order to achieve GH stimulation are familiar to the specialist. For example, arginine, alpha 1 and alpha 2-agonists,

such as clonidine, norepinephrine or salbutamol, glucagon, pyridostigmine, galanine, GH-releasing hormone, NPY (neuropeptide Y) and dopamine agonists, such as apomorphine, quinpirole or cabergoline.

Suitable substances which induce a GH analogous effect include, for instance, GHRP (growth hormone, releasing hexapeptide, hexareline), GH releasing peptide 1, 2, 6 and non-peptidergic agonists of growth hormone releasing peptide such as MK 0677, EP 51389 (2-methylalanyl-2-methyl-D-tryptophyl-2-methyl-D-tryptophanamide), L 692429 (3-amino-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]butanamide], or L 692585 (3-[[(2R)-2hydroxypropyl]amino]-3-methyl-N-[(3R)-2,3,4,5-tetrahydro-2-oxo-1-[[2'-(1H-tetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-1H-1-benzazepine-3-yl]-butanamide).

Suitable substances which promote IGF-I release include, for example, cannabinoide such as e.g. HU-210 (3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6H-dibenzo[b,d]pyran-9-methanol) or serotonine receptor agonists such as e.g. 8-OH DPAT (8-hydroxy-2-dipropylamino)tetraline), or SC 53116 (4-amino-5-chloro-N-[[(1s,7aS)-hexahydro-1H-pyrrolizine-1-yl]methyl]-2-methoxy-benzamide).

Patent Claims

1. Use of growth hormone for manufacture of medicaments for the therapy of female and male sexual functional disorders, such as the lack or loss of libido, problems relating to orgasms, insufficient lubrication, erectile dysfunction for all aetiologies not treated in a causal manner, in cases of insufficient increase in hGH concentration during sexual stimulation and for those with hGH deficiency.

2. Use of growth hormone according to Claim 1 in combination with substances which lead to GH stimulation.

3. Use of growth hormone according to Claim 1 in combination with substances which induce a GH analogous effect.

4. Use of growth hormone according to Claim 1 in combination with substances which promote IGF-I release.

5. Use of substances which lead to GH stimulation according to Claim 1.

6. Use of substances which induce a GH analogous effect according to Claim 1.

7. Use of substances which promote IGF-I release according to Claim 1.

8. Use of growth hormone for the therapy of female and male sexual functional disorders such as lack or loss of libido, problems relating to orgasms, insufficient lubrication, erectile dysfunction for all aetiologies not treated in a causal manner, in cases of insufficient increase in hGH concentration during sexual stimulation and for those with hGH deficiency.

9. Use of substances which lead to GH stimulation according to Claim 8.

10. Use of substances which induce a GH analogous effect according to Claim 8.

11. Use of substances which promote IGF-I release according to Claim 8.

Summary

This innovative breakthrough concerns the use of human growth hormone (hGH, GH) alone or in combination with substances which result in GH stimulation, induce a GH analogous effect or promote IGF-I release for the manufacture of medicaments for the treatment of sexual functional disorders of both sexes and the methods of therapy of the named disorders.

Figure 1: Course of human growth hormone levels in the cavernous (CC = Corpus cavernosum) and the systemic blood (CV = cubital vein) of healthy males during penile flaccidity, tumescence, rigidity, and detumescence. All data are given in ng/mL as mean ± standard deviation of the mean.

Figure 2: Course of hGH serum levels in blood samples taken during different penile conditions (flaccidity, tumescence, detumescence) from the corpus cavernosum (CC) and the cubital vein (CV) of patients suffering from erectile dysfunction.

Figure 3: Relaxation of human corpus cavernosum strips in vitro induced by cumulative addition of recombinant human growth hormone. Each point is expressed as percentage of maximum norepinephrine-HCl - induced tension and represents mean ± standard deviation of the mean of n = 12 determinations.

Figure 4: Stimulating effects of recombinant human growth hormone (rhGH) and sodiumnitroprusside (SNP) on tissue levels of cGMP in isolated human cavernous smooth muscle strips. Each bar represents mean ± standard deviation of the mean of n = 3 - 6 determinations.

Figure 1

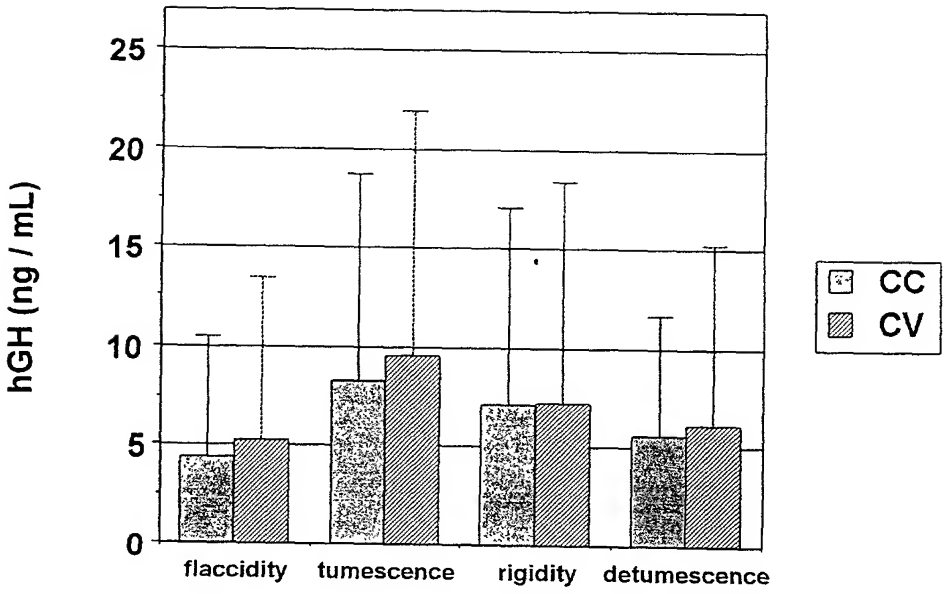


Figure 2

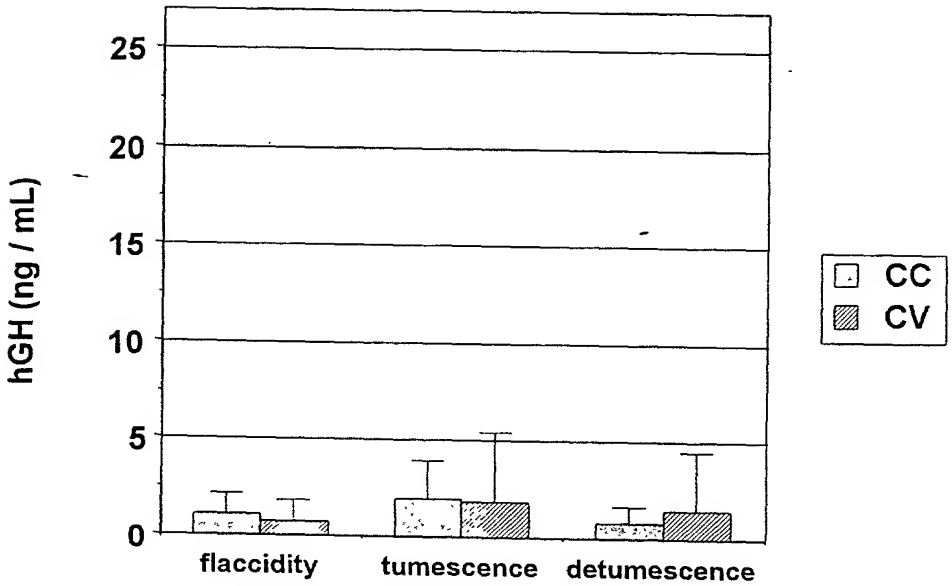


Figure 3

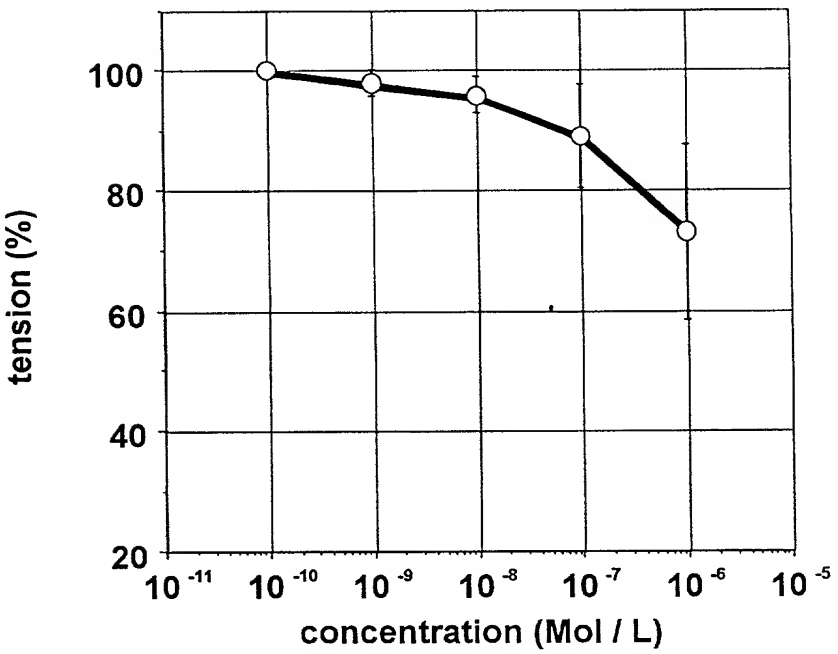
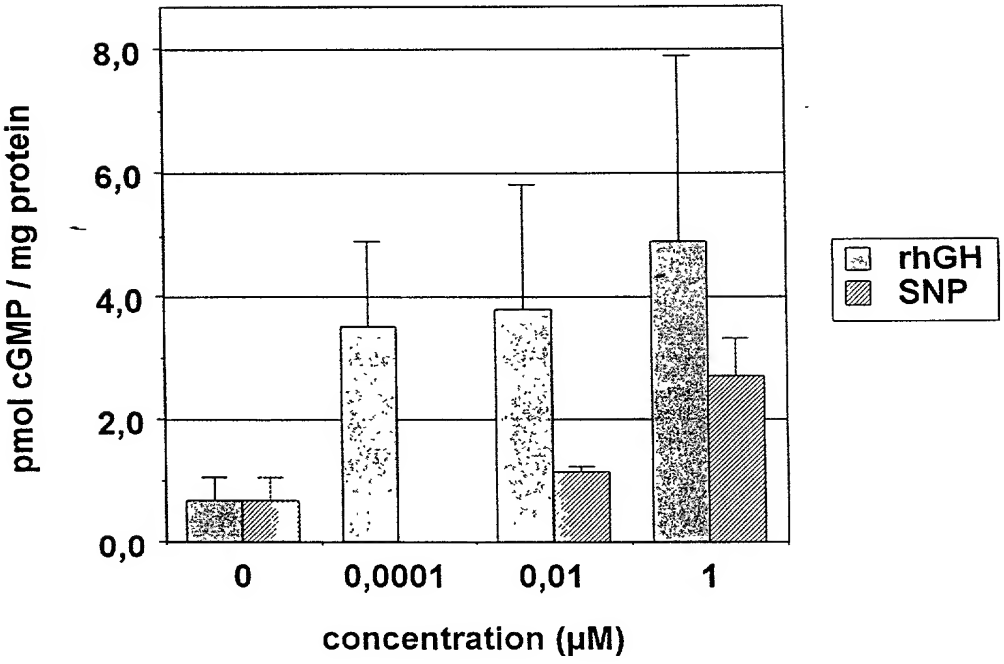


Figure 4



#3

Attorney Docket No. 13390.2USWO

MERCHANT & GOULD P.C.

United States Patent Application

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor I hereby declare that: my residence, post office address and citizenship are as stated below next to my name; that

I verily believe I am the original, first and sole inventor (if only one name is listed below) or a joint inventor (if plural inventors are named below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: USE OF GROWTH HORMONE (HGH) FOR THE TREATMENT OF SEXUAL FUNCTIONAL DISTURBANCES

The specification of which
a. ☒ is attached hereto
b. ☐ was filed on as application serial no. and was amended on (if applicable) (in the case of a PCT-filed application) described and claimed in international no. PCT/EP00/05517 filed June 15, 2000 and as amended on _____ (if any), which I have reviewed and for which I solicit a United States patent.

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I hereby claim foreign priority benefits under Title 35, United States Code, § 119/365 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on the basis of which priority is claimed:

a. ☐ no such applications have been filed.
b. ☒ such applications have been filed as follows:

FOREIGN APPLICATION(S), IF ANY, CLAIMING PRIORITY UNDER 35 USC § 119			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**
GERMANY	199 27 678.1	17/JUNE/1999	
ALL FOREIGN APPLICATION(S), IF ANY, FILED BEFORE THE PRIORITY APPLICATION(S)			
COUNTRY	**APPLICATION NUMBER**	**DATE OF FILING (day, month, year)**	**DATE OF ISSUE (day, month, year)**

I hereby claim the benefit under Title 35, United States Code, § 120/365 of any United States and PCT international application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

U.S. APPLICATION NUMBER	DATE OF FILING (day, month, year)	STATUS (patented, pending, abandoned)

I hereby claim the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below:

U.S. PROVISIONAL APPLICATION NUMBER	DATE OF FILING (Day, Month, Year)

I acknowledge the duty to disclose information that is material to the patentability of this application in accordance with Title 37, Code of Federal Regulations, § 1.56 (reprinted below):

§ 1.56 Duty to disclose information material to patentability.

(a) A patent by its very nature is affected with a public interest. The public interest is best served, and the most effective patent examination occurs when, at the time an application is being examined, the Office is aware of and evaluates the teachings of all information material to patentability. Each individual associated with the filing and prosecution of a patent application has a duty of candor and good faith in dealing with the Office, which includes a duty to disclose to the Office all information known to that individual to be material to patentability as defined in this section. The duty to disclose information exists with respect to each pending claim until the claim is canceled or withdrawn from consideration, or the application becomes abandoned. Information material to the patentability of a claim that is canceled or withdrawn from consideration need not be submitted if the information is not material to the patentability of any claim remaining under consideration in the application. There is no duty to submit information which is not material to the patentability of any existing claim. The duty to disclose all information known to be material to patentability is deemed to be satisfied if all information known to be material to patentability of any claim issued in a patent was cited by the Office or submitted to the Office in the manner prescribed by §§ 1.97(b)-(d) and 1.98. However, no patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through bad faith or intentional misconduct. The Office encourages applicants to carefully examine:

(1) prior art cited in search reports of a foreign patent office in a counterpart application, and

(2) the closest information over which individuals associated with the filing or prosecution of a patent application believe any pending claim patentably defines, to make sure that any material information contained therein is disclosed to the Office.

(b) Under this section, information is material to patentability when it is not cumulative to information already of record or being made of record in the application, and

(1) It establishes, by itself or in combination with other information, a prima facie case of unpatentability of a claim; or

(2) It refutes, or is inconsistent with, a position the applicant takes in:

(i) Opposing an argument of unpatentability relied on by the Office, or

(ii) Asserting an argument of patentability.

A prima facie case of unpatentability is established when the information compels a conclusion that a claim is unpatentable under the preponderance of evidence, burden-of-proof standard, giving each term in the claim its broadest reasonable construction consistent with the specification, and before any consideration is given to evidence which may be submitted in an attempt to establish a contrary conclusion of patentability.

(c) Individuals associated with the filing or prosecution of a patent application within the meaning of this section are:

(1) Each inventor named in the application:

(2) Each attorney or agent who prepares or prosecutes the application; and

(3) Every other person who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application.

(d) Individuals other than the attorney, agent or inventor may comply with this section by disclosing information to the attorney, agent, or inventor.

(e) In any continuation-in-part application, the duty under this section includes the duty to disclose to the Office all information known to the person to be material to patentability, as defined in paragraph (b) of this section, which became available between the filing date of the prior application and the national or PCT international filing date of the continuation-in-part application.

I hereby appoint the following attorney(s) and/or patent agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected herewith:

Albrecht, John W.	Reg. No. 40,481	Leonard, Christopher J.	Reg. No. 41,940
Ali, M. Jeffer	Reg. No. 46,359	Liepa, Mara E.	Reg. No. 40,066
Altera, Allan G.	Reg. No. 40,274	Lindquist, Timothy A.	Reg. No. 40,701
Anderson, Gregg I.	Reg. No. 28,828	Lown, Jean A.	Reg. No. 48,428
Batzli, Brian H.	Reg. No. 32,960	Mayfield, Denise L.	Reg. No. 33,732
Beard, John L.	Reg. No. 27,612	McDonald, Daniel W.	Reg. No. 32,044
Berns, John M.	Reg. No. 43,496	McIntyre, Jr., William F.	Reg. No. 44,921
Branch, John W.	Reg. No. 41,633	Mitchem, M. Todd	Reg. No. 40,731
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Carlson, Alan G.	Reg. No. 25,959	Pauly, Daniel M.	Reg. No. 40,123
Caspers, Philip P.	Reg. No. 33,227	Phillips, John B.	Reg. No. 37,206
Clifford, John A.	Reg. No. 30,247	Pino, Mark J.	Reg. No. 43,858
Cook, Jeffrey	Reg. No. 48,649	Prendergast, Paul	Reg. No. 46,068
Daignault, Ronald A.	Reg. No. 25,968	Pytel, Melissa J.	Reg. No. 41,512
Daley, Dennis R.	Reg. No. 34,994	Qualey, Terry	Reg. No. 25,148
Daulton, Julie R.	Reg. No. 36,414	Reich, John C.	Reg. No. 37,703
DeVries Smith, Katherine M.	Reg. No. 42,157	Reiland, Earl D.	Reg. No. 25,767
DiPietro, Mark J.	Reg. No. 28,707	Samuels, Lisa A.	Reg. No. 43,080
Doscotch, Matthew A.	Reg No. P-48,957	Schmaltz, David G.	Reg. No. 39,828
Edell, Robert T.	Reg. No. 20,187	Schuman, Mark D.	Reg. No. 31,197
Epp Ryan, Sandra	Reg. No. 39,667	Schumann, Michael D.	Reg. No. 30,422
Glance, Robert J.	Reg. No. 40,620	Scull, Timothy B.	Reg. No. 42,137
Goff, Jared S.	Reg. No. 44,716	Sebald, Gregory A.	Reg. No. 33,280
Goggin, Matthew J.	Reg. No. 44,125	Skoog, Mark T.	Reg. No. 40,178
Gotta, Charles E.	Reg. No. 26,896	Spellman, Steven J.	Reg. No. 45,124
Gorman, Alan G.	Reg. No. 38,472	Stewart, Alan R.	Reg. No. 47,974
Gould, John D.	Reg. No. 18,223	Stoll-DeBell, Kirstin L.	Reg. No. 43,164
Gregson, Richard	Reg. No. 41,804	Sullivan, Timothy	Reg. No. 47,981
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Harner, Samuel A.	Reg. No. 46,754	Swenson, Erik G.	Reg. No. 45,147
Hamre, Curtis B.	Reg. No. 29,165	Tellekson, David K.	Reg. No. 32,314
Harrison, Kevin C.	Reg. No. 46,759	Trembath, Jon R.	Reg. No. 38,344
Hertzberg, Brett A.	Reg. No. 42,660	Tunheim, Marcia A.	Reg. No. 42,189
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Hope, Leonard J.	Reg. No. 44,774	Wahl, John R.	Reg. No. 33,044
Jardine, John S.	Reg. No. P-48,835	Weaver, Paul L.	Reg. No. 48,640
Johns, Nicholas P.	Reg. No. 48,995	Welter, Paul A.	Reg. No. 20,890
Johnston, Scott W.	Reg. No. 39,721	Whipps, Brian	Reg. No. 43,261
Kadievitch, Natalie D.	Reg. No. 34,196	Whitaker, John E.	Reg. No. 42,222
Kaseburg, Frederick A.	Reg. No. 47,695	Wier, David D.	Reg. No. P-48,229
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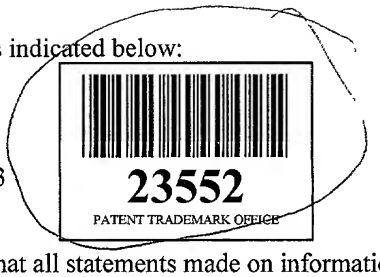
Keys, Jeramie J.	Reg. No. 42,724	Withers, James D.	Reg. No. 40,376
Knearl, Homer L.	Reg. No. 21,197	Witt, Jonelle	Reg. No. 41,980
Kowalchyk, Alan W.	Reg. No. 31,535	Wong, Thomas S.	Reg. No. 48,577
Kowalchyk, Katherine M.	Reg. No. 36,848	Wu, Tong	Reg. No. 43,361
Lacy, Paul E.	Reg. No. 38,946	Young, Thomas	Reg. No. 25,796
Larson, James A.	Reg. No. 40,443	Zeuli, Anthony R.	Reg. No. 45,255

I hereby authorize them to act and rely on instructions from and communicate directly with the person/assignee/attorney/firm/ organization who/which first sends/sent this case to them and by whom/which I hereby declare that I have consented after full disclosure to be represented unless/until I instruct Merchant & Gould P.C. to the contrary.

I understand that the execution of this document, and the grant of a power of attorney, does not in itself establish an attorney-client relationship between the undersigned and the law firm Merchant & Gould P.C., or any of its attorneys.

Please direct all correspondence in this case to Merchant & Gould P.C. at the address indicated below:

Merchant & Gould P.C.
P.O. Box 2903
Minneapolis, MN 55402-0903



I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00	Full Name Of Inventor	Family Name: BECKER	First Given Name: Armin	Second Given Name: Johannes
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4	Mailing Address	Address: Schopenhauer-Str. 27	City: Hannover	State & Zip Code/Country: D-30625 / GERMANY
Signature of Inventor 204:			Date: Jan 7, 2002	